

DIALOG(R) File 155:MEDLINE(R)

09694718 98111853 PMID: 9450183

Identification and characterization of a novel member of the **EXT** gene family, **EXTL2**.

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European journal of human genetics : EJHG (ENGLAND) Nov-Dec 1997, 5 (6) p382-9, ISSN 1018-4813 Journal Code: 9302235

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Recently, two homologous genes, **EXT1** and **EXT2**, with a putative tumor suppressor function have been described. Mutations in both genes are responsible for **multiple exostosis syndrome (EXT)**, an autosomal dominant condition characterized by the presence of **multiple osteochondromas**, bony excrescences that sometimes undergo malignant transformation to chondrosarcoma. This family of **EXT** genes has been extended by the identification of an **EXT-like (EXTL)** gene showing a high degree of homology with the **EXT** genes. We report here a second **EXT-like** gene (**EXTL2**) which is homologous to the **EXT** and **EXTL** genes. **EXTL2** consists of 5 exons encoding an ubiquitously expressed protein of 330 amino acids. In addition, a putative pseudogene, **EXTL2P** was also identified. The **EXTL2** gene was assigned to chromosome 1p11-p12, whereas **EXTL2P** was mapped on chromosome 2q24-q31.

2/3,AB/7 (Item 7 from file: 155)

DIALOG(R) File 155:MEDLINE(R)

08080345 94214436 PMID: 8162019

Assignment of a second locus for **multiple exostoses** to the pericentromeric region of chromosome 11.

Wu Y Q; Heutink P; de Vries B B; Sandkuijl L A; van den Ouweland A M; Niermeijer M F; Galjaard H; Reyniers E; Willems P J; Halley D J

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Human molecular genetics (ENGLAND) Jan 1994, 3 (1) p167-71, ISSN 0964-6906 Journal Code: 9208958

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Hereditary multiple exostoses (EXT) is an autosomal dominant disorder of enchondral bone formation characterized by **multiple bony outgrowths (exostoses)**, with progression to osteosarcoma in a minority of cases. The exclusive involvement of skeletal abnormalities distinguishes **EXT** from the clinically more complex **Langer-Giedion syndrome (LGS)**, which is associated with deletions at chromosome 8q24. Previously, linkage analysis has revealed a locus for **EXT** in the **LGS** region on chromosome 8q24. However, locus heterogeneity was apparent with 30% of the families being unlinked to 8q24. We report on two large pedigrees segregating **EXT** in which linkage to the **LGS** region was excluded. To localize the **EXT** gene(s) in these families we performed a genome search including 254 microsatellite markers dispersed over all autosomes and the X chromosome. In both families evidence was obtained for linkage to markers from the proximal short and long arms of chromosome 11. Two-point analysis gave the highest lod score for D11S554 ($Z_{max} = 7.148$ at $\theta = 0.03$). Multipoint analysis indicated a map position for the **EXT** gene between D11S905 and D11S916, with a peak multipoint lod score of 8.10 at 6 cM from D11S935. The assignment of a second locus for **EXT** to the pericentromeric region of chromosome 11

implicates an area that is particularly rich in genes responsible for developmental abnormalities and neoplasia.

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928 EXT
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631884 MULTIPLE
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2/3,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13585883 22224265 PMID: 12239711

Reevaluation of a genetic model for the development of exostosis in
hereditary multiple exostosis.

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American journal of medical genetics (United States) Sep 15 2002, 112

(1) p1-5, ISSN 0148-7299 Journal Code: 7708900

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: In Process

EXT1 and EXT2 are genes that have been shown to cause **hereditary multiple** exostosis (HME), a **syndrome** marked by the formation of bony growths juxtaposed to the growth plate. These genes are members of a growing family of proteins with glycosyltransferase activity required for the synthesis of heparan sulfate chains. This protein activity is predicted to play a role in the expression of proteoglycans on the cell surface and in the extracellular matrix. We and others have previously suggested that a two-hit mutational model applies to the development of an exostosis where a germline mutation coupled with a somatic mutation results in the loss of EXT1 or EXT2 function and subsequent tumor formation. We report the direct sequencing and loss of heterozygosity (LOH) analysis of 12 **exostoses** from 10 HME families, 4 solitary **exostoses**, and their corresponding constitutional DNA. Of the 16 **exostoses** screened, we find only one solitary case in which two somatic mutations, a deletion and an LOH, are present. This provides limited support for the two-hit hypothesis involving the EXT1 and EXT2 genes for the development of an exostosis. Alternative models are developed based on the functional significance of **EXT** proteins in heparan sulfate biosynthesis. Copyright 2002 Wiley-Liss, Inc.

2/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12810932 21587891 PMID: 11731209

Hereditary multiple exostoses : from genetics to
clinical **syndrome** and complications.

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European journal of radiology (Ireland) Dec 2001, 40 (3) p208-17,

ISSN 0720-048X Journal Code: 8106411

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

OBJECTIVE: To give an overview of genetic, clinical and radiological

aspects in two families over four generations with known **hereditary multiple exostoses** (HME). METHODS AND MATERIAL: After linkage analysis in both families to localize the defective gene, mutation analysis was performed in these genes to identify the underlying mutation. In the 31 affected individuals, location, number and morphology and evolution of exostosis, evolution of remodeling defects at the metaphysis, and the extent of possible complications were evaluated on clinical and imaging (plain radiography, computed tomography (CT), and magnetic resonance imaging (MRI)) data over a lifetime period. RESULTS AND CONCLUSIONS: Both families demonstrate the gene defect in the same **EXT-2** gene locus on chromosome 11p. **Exostoses** are preferentially located in the lower extremity (hip, knee and lower leg), humerus, and forearm. Any other bone may be involved, except for the calvaria of the skull and the mandible. **Exostoses** are rather sessile than pedunculated. Exostosis is rarely present at birth but develops gradually and may persist to grow slowly after closure of the growth plates. Preferential expression of the remodeling defect was seen in the hip, distal femur (trumpet-shaped metaphysis) and forearm (shortening of the ulna with secondary bowing of the radius and development of a pseudo-Madelung deformity). These radiological manifestations start at the age of 4-5 years and become more obvious as the enchondral bone formation progresses with age. Reported complications in these families consist of local entrapment phenomena (vessel, tendon, nerve), frictional bursitis, and sarcomatous transformation. MRI was able to suggest these complications and is the imaging technique of choice in the evaluation of symptomatic **exostoses**.

2/3,AB/3 (Item 3 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

10484828 20003090 PMID: 10529789

New perspectives on the molecular basis of **hereditary** bone tumours.
McCormick C; Duncan G; Tufaro F
Department of Microbiology and Immunology, University of British Columbia, Vancouver, Canada V6T 1Z3.
Molecular medicine today (ENGLAND) Nov 1999, 5 (11) p481-6, ISSN 1357-4310 Journal Code: 9508560
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Bone development is a highly regulated process sensitive to a wide variety of hormones, inflammatory mediators and growth factors. One of the most common **hereditary** skeletal dysplasias, **hereditary multiple exostoses** (HME), is an autosomal dominant disorder characterized by skeletal malformations that manifest as bony, benign tumours near the end of long bones. HME is usually caused by defects in either one of two genes, **EXT1** and **EXT2**, which encode enzymes that catalyse the biosynthesis of heparan sulphate, an important component of the extracellular matrix. Thus, HME-linked bone tumours, like many other skeletal dysplasias, probably result from disruptions in cell surface architecture. However, despite the recent success in unravelling functions for several members of the **EXT** gene family, significant challenges remain before this knowledge can be used to develop new approaches for the diagnosis and treatment of disease.

2/3,AB/4 (Item 4 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

10386414 99368838 PMID: 10439965

Molecular and clinical examination of an Italian **DEFECT11** family.
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European journal of human genetics : EJHG (ENGLAND) Jul 1999, 7 (5)
p579-84, ISSN 1018-4813 Journal Code: 9302235

Document type: Journal Article

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Main Citation Owner: NLM

Record type: Completed

The **DEFECT11 syndrome** is a contiguous gene syndrome associated with deletions in the proximal part of chromosome 11p. In this study, we describe in an Italian family the co-existence of **multiple exostoses (EXT)** and enlarged parietal foramina (FPP), the two major symptoms of this **syndrome**, with abnormalities of the central nervous system. The latter may be a yet undescribed feature of **DEFECT11 syndrome**. FISH and molecular analysis allowed us to identify a small deletion on 11p11-p12, further refining the localisation of the FPP gene involved in the **DEFECT11 syndrome**.

2/3,AB/5 (Item 5 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

10384719 99375021 PMID: 10441575

EXT-mutation analysis and loss of heterozygosity in sporadic and **hereditary** osteochondromas and secondary chondrosarcomas.

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American journal of human genetics (UNITED STATES) Sep 1999, 65 (3)
p689-98, ISSN 0002-9297 Journal Code: 0370475

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Osteochondromas occur as sporadic solitary lesions or as **multiple** lesions, characterizing the **hereditary multiple exostoses syndrome (EXT)**. Approximately 15% of all chondrosarcomas arise within the cartilaginous cap of an osteochondroma. **EXT** is genetically heterogeneous, and two genes, **EXT1** and **EXT2**, located on 8q24 and 11p11-p12, respectively, have been cloned. It is still unclear whether osteochondroma is a developmental disorder or a true neoplasm. Furthermore, it is unclear whether inactivation of both alleles of an **EXT** gene, according to the tumor-suppressor model, is required for osteochondroma development, or whether a single **EXT** germline mutation acts in a dominant negative way. We therefore studied loss of heterozygosity and DNA ploidy in eight sporadic and six **hereditary** osteochondromas. **EXT1**- and **EXT2**-mutation analysis was performed in a total of 34 sporadic and **hereditary** osteochondromas and secondary peripheral chondrosarcomas. We demonstrated osteochondroma to be a true neoplasm, since aneuploidy was found in 4 of 10 osteochondromas. Furthermore, LOH was almost exclusively found at the **EXT1** locus in 5 of 14 osteochondromas. Four novel constitutional cDNA alterations were detected in exon 1 of **EXT1**. Two patients with **multiple** osteochondromas demonstrated a germline mutation combined with loss of the remaining wild-type allele in three osteochondromas, indicating that, in cartilaginous cells of the growth plate, inactivation of both copies of the **EXT1** gene is required for osteochondroma formation in **hereditary** cases. In contrast, no somatic **EXT1** cDNA alterations were found in sporadic osteochondromas. No mutations were found in the **EXT2** gene.

2/3,AB/6 (Item 6 from file: 155)